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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/349,915 | 07/08/1999 | Carl H. June | 36119-125US10 | 7335 |

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| EXAMINER | |
|---|---|
| GAMBEL, PHILLIP | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1644 | |

DATE MAILED: 03/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/349915 | Applicant(s) JUNE |
|---|---|---|
| | Examiner GAMBEL | Art Unit 1644 |

*-- Th MAILING DATE of this communication appears on th cover sheet with the c rresp ndence address --*

**Peri d f r R ply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☑ Responsive to communication(s) filed on 11/27/02

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disp sition of Claims**

4)☑ Claim(s) _____ is/are pending in the application. 1, 50-59

4a) Of the above claim(s) _____ is/are withdrawn from consideration. 56, 59

5)☐ Claim(s) _____ is/are allowed.

6)☑ Claim(s) _____ is/are rejected. 1, 50-55, 57, 58

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☑ The drawing(s) filed on 11/27/02 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Pri rity under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☑ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☑ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☑ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

1. Applicant's election of the species of anti-CD28 antibodies with traverse in Paper No. 24, filed 11/27/02, is acknowledged. The traversal is on the grounds that it would not be unduly burdensome. As pointed out in the previous Office Action (Paper No. 22), the species CD28-specific antibodies and B7-1 are distinct because their structures and physicochemical properties differ to the extent that a person of ordinary skill in the art would not envision one in view of the other. Therefore, they are separate and patentably distinct species. It is noted the written support and enablement of CD28-specific antibodies and B7-1 differ as well as requiring non-coextensive searches.

Again, it is noted that should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Given that applicant does not admit or provide evidence the species are obvious variants, the species requirement is maintained for the reasons of record.

For examination purposes, claims 1, 50-55 and 57-58 are under consideration as they read on the use of CD28-specific antibodies as the elected species.

Claims 56 and 59 are withdrawn from consideration as being drawn to the non-elected species.

Claims 2-49 have been canceled previously.

2. Formal drawings, filed 11/27/02 (Paper No. 25), comply with 37 CFR 1.84.

3. The priority of the instant claims appears to be USSN 08/253,964, filed 6/3/94, as the previous applications do not appear to provide written description for the generic terms of "agents"/" first agent"/"second agent"; for the "agent"/"ligand"/"second agent" stimulating an accessory molecule; for "ex vivo" as well as "having directly immobilized thereon (a) first agent ... and (b) a second agent ... ".

With respect to claims 50-59, the filing date of the instant claims is deemed to be the filing date of the priority application USSN 08/253,964, filed 6/3/94, as the previous priority applications do not provide written description of "immobilizing anti-CD3 antibodies and anti-CD28 on the same solid phase", as indicated by the claimed recitation "having directly immobilized thereon (a) first agent ... and (b) a second agent ... ".

Applicant is invited to clarify the priority of the instant claims. If applicant desires priority prior to 6/3/94; applicant is invited to point out and provide documentary support for the priority of the instant claims.

Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

Entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977)

Since there may be ambiguity over the priority of the instant claims, rejections based upon different dates are made with respect to the instant claims.

4. If applicant desires priority under 35 U.S.C. 120 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No._____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

Applicant should update the status of the priority documents.

Further, it is noted that the priority document "08/253,694" should be "08/253,964'".

5. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

Trademarks should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office Action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined *under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).*

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

8. Claim 1 is rejected under 35 U.S.C. § 102(b) as being anticipated by Ledbetter et al. (J. Immunol. 137: 3299-3305, 1986) (1449; #B13) (see entire document). Ledbetter et al. teach methods of activating the proliferation of T cells with anti-CD3 and anti-Tp44 antibodies (e.g., see Abstract, Results and Discussion). Anti-Tp44 antibodies are the same or equivalent of anti-CD28 antibodies. Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods to stimulate T cells with anti-CD3 antibodies and anti-Tp44 (anti-CD28) antibodies.

9. Claims 50-55 are rejected under 35 U.S.C. § 102(e) as being anticipated by Ledbetter et al. (U.S. Patent No. 6,010,902) (see entire document). Ledbetter et al. teach compositions comprising heteroconjugates or bispecific antibodies comprising antibodies, including antibodies to human CD antigens involved in T cell activation, including antibodies to CD3 in combination with anti-CD28 antibodies (e.g. 9.3), including compositions in order to stimulate T cell populations and subpopulations and reinfused in patients (e.g. see columns 15-16) (see entire document, including Detailed Description of the Invention and Examples). The Detailed Description of the Invention provides various teachings that these cell populations have increased signal transduction, which can be measured by various known assays. Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods to stimulate T cell populations with heteroconjugates comprising anti-CD3 and anti-CD28 antibodies.

10. Claims 50-55 and 57-58 are rejected under 35 U.S.C. § 103 as being unpatentable over Ledbetter et al. (EP0440373; 1449, #A2) AND/OR Ledbetter et al. (U.S. Patent No. 6,010,902) in view of Chang (U.S. Patent No. 6,129,916; 1449).

Ledbetter et al. (EP0440373) teach methods of activating T lymphocytes with immobilized anti-CD3 and immobilized anti-CD28 antibodies, including whole antibodies, where the anti-CD3 antibodies are immobilized on the solid supports, including Sepharose beads and the anti-CD28 is cross-linked by a variety of means, including immobilized to plastic surfaces (see entire document, including Contact with CD3 or CD28 Antibody and Crosslinking on page 4 and Claims, e.g. claims 1, 9, 20). Ledbetter et al. provide an Example of culturing for three days (page 6, last paragraph) and teaches preparing cells for adoptive immunotherapy (page 4, Therapy).

Ledbetter et al. (EP0440373) differ from the claimed methods by not exemplifying combining anti-CD28 and anti-CD3 antibodies on the same plate; however it is clear that Ledbetter et al. do teach combining both specificities to stimulate T cells and to immobilize both antibodies on plastic surfaces.

Ledbetter et al. ('902) teach compositions comprising heteroconjugates or bispecific antibodies comprising antibodies, including antibodies to human CD antigens involved in T cell activation, including antibodies to CD3 in combination with anti-CD28 antibodies (e.g. 9.3), including compositions in order to stimulate T cell populations and subpopulations and reinfused in patients (e.g. see columns 15-16) (see entire document, including Detailed Description of the Invention and Examples). The Detailed Description of the Invention provides numerous teachings that these cell populations have increased signal transduction, which can be measured by various known assays.

In further support of the teachings of Ledbetter et al. ('902), Chang provides a clear teaching of combining the particular CD3 and CD28 specificities, by teaching the use of microbeads and cross-linking by well-established manner (columns 7-8) in cross-linking anti-CD3 and anti-CD28 antibodies on microbeads to activate T cells in vivo (see entire document, including Summary of the Invention and Detailed Description of the Invention).

Although it is noted that Chang focuses on the in vivo administration of stimulating immunoconjugates; Chang clearly that it was known to stimulate T cells in vitro via immobilized stimuli (see Background of the Invention). Further, both Ledbetter et al. References teach stimulating T cells for adoptive immunotherapy via CD3 and CD28 stimulation.

As noted previously, it was an art known practice to monitor cell proliferation of interest, including cell size and cell markers at the time the invention was made; as such criteria were known parameters of cell activation. Also, it was common practice at the time the invention was made to re-activate and re-stimulate cells to maintain proliferation and expansion of cell populations of interest at the time the invention was made. Here, both Ledbetter et al. references teach methods of preparing cells for adoptive immunotherapy, which required large numbers of cells resulting from multiple stimulation.

Therefore, one of ordinary art at the time the invention was made would have expected to monitor the proliferation of said T cells by various parameters and to re-stimulate T cells undergoing expansion to achieve large number of cells of interest. It is noted that applicant has not seasonally traversed this aspect of the rejections of record.

One of ordinary skill in the art at the time the invention was made would have been motivated to stimulate T cell activation with both CD3-/CD28-specific antibodies, including covalently linking both stimuli to the same solid phase surface, to increase T cell proliferation and numbers of T cells of interest for various purposes, such as T cell studies and adoptive immunotherapy. One of ordinary skill in the art at the time the invention was made would have been motivated to provide immobilized CD3 and CD28 signaling simultaneously on the same plate as an efficient means to stimulate T cells over extended periods of times to grow T cells of interest, including growing large numbers of T cells for adoptive immunotherapy in the treatment of certain diseases and conditions, as taught by the Ledbetter et al. references. The ordinary artisan was motivated to monitor the activation of T cells by the known practices of monitoring cell size and cell surface markers to measure said T cell activation at the time the invention was made. To achieve large numbers of cells or maintain activated T cells, it was routinely practiced by the ordinary artisan at the time the invention was made to re-stimulate or re-activated T cells with the appropriate stimuli. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary

. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

11. The non-statutory double patenting rejection, whether of the obvious-type or non-obvious-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (b) and © may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFfR 1.78 (d).

Effective January 1, 1994, a registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 50-55 and 57-58 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over
claims 86-89, 92-94, 96, 102-106, 108-115, 118-, 120, 122, 128-131, 135-138, 141-148 and 150-167 of commonly assigned copending USSN 08/253,964;
claims 57-62, 69-72 and 75-77 of commonly assigned copending USSN 08/592,711;
claims 1, 46, 47, 54-58 and 69-72 of commonly assigned copending USSN 09/183,055;
claims 1 and 50-55, 57-58 of commonly assigned copending USSN 09/3352,202; and
claims 10 and 50-56, 58-67 and 69-84 of commonly assigned copending USSN 09/553,865.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant and copending claims appear to rely upon the same or nearly the same method steps and ingredients, particularly the use of anti-CD3 and anti-CD28 antibodies to stimulate and expand T cells.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. Claims 50-55 and 57-58 are directed to an invention not patentably distinct from
claims 1, 46, 47, 54-58 and 69-72 of commonly assigned copending USSN 09/183,055;
for the reasons set forth above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned , discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 CFR 1.78(c) and 35 U.S.C. 132 to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

14 Claims 50-55 and 57-58 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-32 of U.S. Patent No. 6,352,694. Although the conflicting claims are not identical, they are not patentably distinct from each other because the pending and patented claims are drawn to the same or nearly the same methods of stimulating T cells with anti-CD3 and anti-CD28 antibodies and, in particular, the patented claims anticipate the instant claims.

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

PHILLIP GAMBEL

Phillip Gambel, PhD.
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Technology Center 1600
March 17, 2003